REMARKS/ARGUMENTS

Claims 10-12, 14 and 18-21 are pending herein. Claims 10-12 have been amended to better describe the invention and to patentably distinguish over the cited art. Claim 10 has been revised to indicate a specific step of amelioration of the diffuse macular edema in the patient being treated. New claims 18-21 have been added with the independent claim 18 also calling for a consequent inhibition of a deterioration of visual acuity of the treated subject.

The Examiner had questioned the difference between diabetic retinopathy and diabetic maculopathy in the Office Action and had raised a number of points appearing at pages 2-5 of that Office Action. Applicants address those points in the reply as well as in the enclosed Rule 132 Declaration by Dr. Mara Lorenzi, an unquestioned expert in the field; the Examiner is referred to that Declaration and the doctor's credentials recited therein.

1. The rejection of claims 2-12 and 14 under §102/§103 over Mylari, if applied to the claims as amended, is respectfully traversed.

The Examiner asserts that the reference is pertinent because allegedly the active treating steps are the same and that the reference therefore teaches the claimed invention. As indicated previously, the independent claim (10) has been changed to positively recite the treatment of the present invention and the claims patentably define thereover in both a §102(b) and §103(a) sense.

The term "prevent blindness" is not merely a paraphrase of the term "prevent and ameliorate deterioration of visual acuity". These two terms or expressions do not mean the same thing and are clearly different from each other in pathological conditions. That is, the therapy to prevent blindness is given to patients with diabetic retinopathy because blindness (loss of light perception) is a problem in diabetic retinopathy. On the other hand, the therapy to prevent and ameliorate deterioration of visual acuity is given to patients with diabetic maculopathy because deterioration of visual acuity (a severe blurred vision, doubling of the visual angle, or the like) becomes a problem in diabetic maculopathy. In these two diseases, similar terms are used, which often leads to misunderstanding. The term "blindness" used in diabetic retinopathy means loss of light perception, and it does not refer to the level of visual acuity. On the contrary, the term "deterioration of visual acuity" used in diabetic maculopathy does not mean loss of light perception. As for the terms, these two diseases

have been falsely described in some references and they have not been clearly distinguished from each other in some references. However, the truth is as described above and the attached Declaration of Dr. Lorenzi (see Declaration, page 9, 5, paragraph 1) establishes that fact.

As for the phrase containing "not a few" (Office Action dated January 29, 2009, page 3, line 9), Applicants mistakenly used the term "retinopathy" in the phrase and this part should have been described as "retinopathy which requires the therapy as retinopathy". Namely "severe diabetic retinopathy" is intended. The correct description is as follows: "not a few patients having maculopathy without having severe diabetic retinopathy". That is, some patients having maculopathy do not have severe diabetic retinopathy. Those patients require the therapy only as maculopathy. Applicants apologize for the error. As pointed out by the Examiner, the patient with diabetic maculopathy and the patient with diabetic retinopathy are overlapping each other because, diabetic maculopathy is considered as a "complication" of diabetic retinopathy. With reference to this matter, see Dr. Lorenzi's Declaration (page 9, 5, paragraph 1).

Then, with reference to experimental animal models, Akita[1] indicates a rat model with focal retinal edema to which intraocular pressure is not increased. In the specification, Applicants described the rat model with diffuse retinal edema to which intraocular pressure was increased. Although rats have no macula lutea, the rat model with diffuse retinal edema produced in a visual cell layer corresponding to macula lutea (see enclosed Fig. 1) is considered to be useful as an animal model of diabetic maculopathy. Therefore, Applicants used it. The model is a novel rat model established by Applicants in which edema is produced in the visual cell layer. On the other hand, the monkey model, which was described in the Kato Declaration submitted July 16, 2008, was firstly established based on the rat model in the same method as described above by Applicants. Since monkeys have macula lutea, they are important as models which enable one to predict the effects in humans. A comparative experiment in humans is difficult to conduct. Therefore, the comparative experiment of SNK-860 and Epalrestat was conducted by using the monkey model closer to a

[1] Akita et al., "Effects of an Aldose Reductase Inhibitor, SNK-860, on the Histopathological Changes of Retinal Tissues in a Streptozotocin-Induced Diabetic Rat Model", Acta Med Okayama, 1993, 47, p. 299-304 *(cited in January 29, 2009 Office Action)*

human in order to predict differences in effects in humans. Further, the information "ARI has a good effect on animals, but it does not have an effect on humans" has been described in the Speicher article[2] (at p. 242, Col. 1, paragraph 1). Thus, the comparative experiment in rats may lack persuasion in whether or not the comparative data obtained from rats can be directly applied to humans. There was no experimental animal model for diabetic maculopathy at the time the application was filed. Under such circumstances, there was no motivation to try to determine if ARI had an effect on diabetic maculopathy. The Examiner's recognition as to the purpose of animal models is correct. As described above, ARI has been found effective for animals, but it is not effective for humans. Thus, the importance of animal models is open to question, especially in ARIs, but usually, a simple experiment using a rat model would be carried out initially in this case. There is no doubt that a monkey model would be used next if a good effect is observed in the rat experiment and a human trial would be conducted thereafter if a remarkable effect is observed in the monkey experiment. Therefore, Applicants respectfully submit that no contradictory comments were made as to the experimental animal models. However, Applicants apologize for the misleading expression and the insufficient description.

With reference to the Speicher article, ARI exhibits a strong activity in animal and cellar experiments and thus it would not be surprising even if there is an idea that effectiveness may be found out in optimal designs of clinical studies and with more statistical power. However, in several Phase II/III clinical trials with the drug sorbinil, no efficacy was observed in mild diabetic retinopathy (namely non-proliferative retinopathy) in which the efficacy of sorbinil could be expected[3]. Under the present circumstances, the fact remains that it was not effective for humans. On that basis, it is suggested that ARI will not have an efficacy on humans. Applicants respectfully submit that, in the U.S., nor elsewhere in the world, there is neither an injectable nor oral agent on the market after being subjected to clinical trials for diabetic maculopathy. In spite of a significant unmet medical need, any clinical trial of ARI in patients with diabetic maculopathy has not been carried out. This fact supports the non-obviousness of the present invention. On the other hand, as for SNK-860 whose effectiveness could not be demonstrated in clinical trials for non-proliferative

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[2] Speicher et al., "Pharmacologic Therapy for Diabetic Retinopathy", Expert Opinion on Emerging Drugs, Vol. 8, No. 1, 2003, p. 239-250 *(filed with December 11, 2008 Amendment)*

[3] Sorbinil Retinopathy Trial Research Group, "A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy", Arch Ophthalmol, 1990; 108: p. 1234-1244 *(copy attached)*

retinopathy, Applicants succeeded in demonstrating a high effectiveness of SNK-860 in the clinical trial of diabetic maculopathy for the first time in the world. This is an unexpected result as well as a surprising result. The rejection should be withdrawn.

2. The rejection of claims 10-12 and 14 under §103 over Akita in view of Wani is also respectfully traversed.

Wani has stated that diabetic macular edema (diabetic maculopathy) is related to diabetic retinopathy and these two diseases overlap each other. However, this fact does not deny that diabetic maculopathy is distinct from diabetic retinopathy. From a clinical point of view, diabetic macular edema is recognized not as an accompanying symptom of diabetic retinopathy, but as a different disease. This is obvious from the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scale[4] proposed in about 1990 and the international classification presented by the American Academy of Ophthalmology (AAO) in 2002. In the ETDRS scale, edema is not placed in a standard classification of diabetic retinopathy and it is separately classified as a concept of Clinically Significant Macular Edema (CSME)[5]. In the international classification, diabetic retinopathy and diabetic macular edema are presented separately (see the enclosed Tables 1 and 2). Further, the treatment for diabetic macular edema (diabetic maculopathy) is fundamentally different from the treatment for diabetic retinopathy as described in the specification. Therefore, it is clear that these diseases should be recognized as different from each other. Evidence that these diseases are different in susceptibility to a drug can be found from the fact that PKCβ inhibitor (Ruboxistaurin), i.e., another ophthalmological drug, could not control the development of diabetic retinopathy; however, it exhibited an efficacy on visual impairment of patients with diabetic macular edema[6]. Thus, it is clear that diabetic macular edema (diabetic maculopathy) and diabetic retinopathy are recognized as different from each other. Diabetic retinopathy and diabetic maculopathy are two different diseases and their therapies are

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[4] Early Treatment Diabetic Retinopathy Study Research Group. "Fundus photographic risk factor for progression of diabetic retinopathy", ETDRS Report Number 12, Ophthalmology 1991; 98: p. 823-833 *(copy attached)*

[5] Early Treatment Diabetic Retinopathy Study Research Group. "Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema", ETDRS Report Number 2, Ophthalmology 1987; 94: p. 761-774 *(copy attached)*

[6] The PKC-DRS Study Group, "The Effect of Ruboxistaurin on Visual Loss in Patients with Moderately Severe to Very Severe Nonproliferative Diabetic Retinopathy". Diabetes, 2005, 54: p. 2188-2197 *(filed with July 16, 2008 Amendment)*

different from each other, which is described in the Dr. Lorenzi's Declaration at pages 9-10, 5.1),(a),(b),(c)) and also in Mohamed[7].

Further, the Examiner stated that many reports do not distinguish the various forms but only discuss macular edema. However, in the previously-cited reference by Lopes de Faria, the importance of the treatment of diffuse macular edema is disclosed, e.g., in the sentences "The ability of laser therapy to stabilize or restore the visual acuity in diffuse macular edema is not as good as in focal macular edema, and may result in central vision loss. (p. 173, Col. 2, paragraph 3)", "In contrast, diffuse macular edema in which extensive leakage from the posterior retinal capillary bed is observed, is more difficult to manage and the use of laser photocoagulation is not as efficient as in focal edema. (p. 170, Col. 3, paragraph 4)", and "The results demonstrate that adult-onset DM, HBP, cardiovascular disease, vitreomacular adhesion and severe DR were associated with increased risk of development diffuse macular edema in diabetic patients in comparison with focal macular edema. We suggest that in further studies of diabetic macular edema, the distinction between focal and diffuse forms should be addressed, since the pathogenesis of both processes may not be the same. (p. 174, Cols. 1-2)". In the article by Pedro Romero Aroca[8], the importance of the distinction between diffuse macular edema and focal macular edema in the treatment is disclosed, e.g., in the sentences "The group of patients with focal macular edema was epidemiologically similar to the group of patients without macular edema, and these two groups were quite different epidemiologically to the group of patients with diffuse macular edema. (p. 215, Col. 1, paragraph 5)", additionally, "The importance in determining the factors of epidemiological risk for diffuse and focal macular edema is based on the unsuccessful treatment that currently applied for diffuse macular edema. (p. 214, Col. 1, paragraph 3)". Regarding the important of the distinction between diffuse macular edema and focal macular edema, Lopes de Faria also disclosed that "[t]he importance of classifying the diabetic macular edema into focal and diffuse lies in their different pathological processes. (p. 173, Col. 2, paragraph 3)". Therefore, the therapy for diffuse macular edema is important from the viewpoint of diabetic maculopathy therapy, just as important is how to

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[7] Q Mohamed, et al., "Management of diabetic retinopathy: A systematic review", JAMA 2007; 298:902-916 *(copy attached)*

[8] Aroca et al., "Risk Factors for Diffuse and Focal Macular Edema". J Diab Complications 2004, 18: p. 211-215 *(filed with July 16, 2008 Amendment)*

treat the patient with diffuse macular edema. In this regard, see Dr. Lorenzi's Declaration at page 10, paragraph 1.

As stated above, the focal retinal edema of diabetic simple retinopathy and the diffuse type of diabetic macular edema are obviously different and have different qualities. Therefore, an effect on the former does not suggest an effect on the latter. Moreover, as explained above, diabetic maculopathy and diabetic retinopathy are different diseases. Therefore, it is not obvious that SNK-860 is effective for the diffuse type of diabetic macular edema from the combination of Akita which discloses that "SNK-860 is effective for focal retinal edema of diabetic simple retinopathy" and Wani which discloses that "diabetic macular edema is associated with diabetic retinopathy and both are overlapping". In addition, Epalrestat, effective for diabetic retinopathy (see Hotta et al.[9]), showed no effect on the monkey model with diabetic maculopathy. On the other hand, SNK-860 not only showed a significant effect on the monkey model with diabetic maculopathy, but also had a remarkable effect in human trials. These are surprising effects for the person skilled in the art as well as effects far beyond expectations, which prove that the invention is non-obvious. In this regard, see Dr. Lorenzi's Declaration at page 10, paragraph 3.

The Examiner is respectfully requested to confirm receipt and consideration of the Information Disclosure Statement filed May 26, 2009.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, the Examiner is herein requested to call Applicants' attorney at the phone number noted below.

[9] Hotta et al., "Diabetic Retinopathy- Experimental and Clinical Approaches from Polyol Pathway". Current Concepts of Aldose Reductase and Its Inhibitions. Amsterdam: Elsevier Science Publishers B.V.; N. Sakamoto et al., editors, 1990: p. 169-177 *(filed with July 16, 2008 Amendment)*

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

June 29, 2009
Date

Stephen P. Burr
Reg. No. 32,970

SPB/CW/tlp

Attachments:
- Tables 1 and 2
- Fig. 1
- Sorbinil Retinopathy Trial Research Group, "A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy", Arch Ophthalmol, 1990; 108: p. 1234-1244
- Early Treatment Diabetic Retinopathy Study Research Group. "Fundus photographic risk factor for progression of diabetic retinopathy", ETDRS Report Number 12, Ophthalmology 1991; 98: p. 823-833
- Early Treatment Diabetic Retinopathy Study Research Group. "Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema", ETDRS Report Number 2, Ophthalmology 1987; 94: p. 761-774
- Q. Mohamed et al., "Management of diabetic retinopathy: A systematic review", JAMA 2007; 298:902-916
- R. Klein et al., Ophthalmology. 1995; 102: 7-16 (cited in Dr. Lorenzi's Declaration)
- R. Klein et al., Ophthalmology. 1998; 105:1801-1815 (cited in Dr. Lorenzi's Declaration)

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Table 1. Diabetic Retinopathy Disease Scale

(http://one.aao.org/CE/PracticeGuidelines/ClinicalStatements_Content.aspx?cid=5e96758f-c10d-41aa-a9b2-fc4d4faac6b9)

International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe NPDR
Severe nonproliferative diabetic retinopathy	Any of the following: • More than 20 intraretinal hemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants **And** no signs of proliferative retinopathy
Proliferative diabetic retinopathy	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy

Table 2. Diabetic Macular Edema Scale

(http://one.aao.org/CE/PracticeGuidelines/ClinicalStatements_Content.aspx?cid=5e96758f-c10d-41aa-a9b2-fc4d4faac6b9)

International Clinical Diabetic Macular Edema Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	**Findings Observable upon Dilated Ophthalmoscopy***
Diabetic macular edema present	• Mild diabetic macular edema: Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
	• Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center
	• Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.

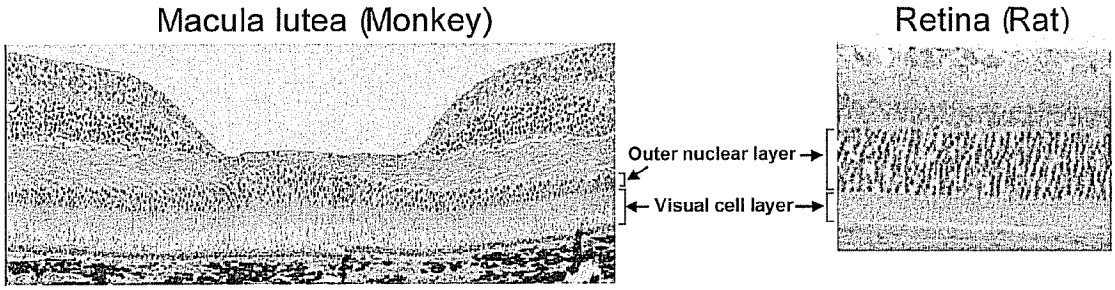

Fig. 1 Structures of macular lutea and retina

A visual cell layer exists both in a macular lutea and a retina, but a macular lutea exists in monkey, not in rat.